EVALUATION OF ANTIMICROBIAL STEWARDSHIP PROGRAMS IMPLEMENTATION AND OUTCOMES IN SELECTED HOSPITALS AT MAKKAH REGION, KINGDOM OF SAUDI ARABIA

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by

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DEDICATION

This thesis is dedicated to my beloved Prophet Mohammad (peace be upon him). As regards, all standards by which human greatness may be measured, we can say it for sure; there is no man greater than Him.

Further, I dedicate this thesis to my beloved parents and my beloved wife. This achievement would have been impossible without their support and unconditional love.

ACKNOWLEDGEMENT

As this is the only part of a thesis that perhaps 95% of those who get a copy of it will ever read, I decided to put it at the beginning. First and foremost, I would like to thank almighty Allah for giving me the strength to complete my PhD studies. I would like to express my deepest gratitude to my supervisor Prof. Dr. Mohamed Azmi Ahmad Hassali. He stood beside me when I missed my family, was always available as a friend and was exceedingly supportive even when I was going off in all directions.

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"May Allah bless all of you"

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LIST OF ABBREVIATIONS

Antimicrobial Stewardship Programs	ASPs
Antimicrobial Resistance	AMR
Arabian-American Oil Company	ARAMCO
Blood Stream Infections	BSI
Carbapenem-Resistant Enterobacteriaceae	CRE
Centers for Diseases prevention and Control	CDC
Chronic Obstructive Pulmonary Disease	COPD
Clinical and Laboratory Standards Institute	CLSI
Coagulase Negative Staphylococci	CNS
Continuous Medical Education	CME
Computerized Prescription Order Entry System	CPOE
Computerized Decision Supports System	CDSS
Critical Care Unit	CCU
Define Daily Dose	DDD
European Society of Clinical Microbiology and Infectious Diseases	ESCMID
Extended Spectrum β-lactamase	ESBLs
Gram Negative Bacterium	GNB
Gram Positive Bacterium	GPB
Infectious Diseases Society of America	IDSA
Intensive Care Unit	ICU
Joint Commission International	JCI
Kingdom of Saudi Arabia	KSA
Klebsella Pneumonia Carbapenemase	KPC

Methicillin sensitive *Staphylococcus auerus*	MSSA
Methicillin Resistant *Staphylococcus auerus*	MRSA
Multi Drug Resistant *Acinetobacter Baumannii*	MDR-AB
Multi Drug Resistant Organisms	MDRO
Ministry of Health	MOH
New Delhi Metallo-β-Lactamase	NDM-1
Pharmacokinetics/Pharmacodynamics	PK/PD
Saudi Central Board of Accreditation of Healthcare Institution	CBAHI
Saudi National Formulary	SNF
Saudi Food & Drug Administration	SFDA
World Health Organization	WHO

GLOSSARY OF KEY TERMS

Terms	Definitions
Antimicrobial Stewardship Program(ASP)	The antimicrobial stewardship program promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms.
Antimicrobial Resistance (AMR)	Multidrug-resistant organisms are bacteria and other microorganisms that have developed resistance to antimicrobial drugs. Common examples of these organisms include MRSA (methicillin/oxacillin-resistant *Staphylococcus aureus*) and VRE (vancomycin-resistant enterococci).
Multidrug-Resistant Organisms (MDRO)	Multidrug-resistant organisms are bacteria and other microorganisms that have developed resistance to antimicrobial drugs. Common examples of these organisms include MRSA (methicillin/oxacillin-resistant *Staphylococcus aureus*) and VRE (vancomycin-resistant enterococci).
Beta-Latamases	Beta-lactamases (β-lactamases, also known as penicillinase) are enzymes (EC 3.5.2.6) produced by bacteria, that provide multi-resistance to β-lactam antibiotics such as penicillins, Cephalosporins, cephamycins, and carbapenems (ertapenem), although carbapenems are relatively resistant to beta-lactamase
Defined Daily Dose	The defined daily dose (DDD) is a statistical measure of drug consumption, defined by the World Health Organization (WHO). It is used to standardize the comparison of drug usage between different drugs or between different health care environments. The DDD is not to be confused with the therapeutic dose or with the dose prescribed by a physician for an individual patient

PENILAIAN TERHADAP PELAKSANAAN PROGRAM PENGAWASAN ANTIMIKROBIAL DAN HASILNYA DI HOSPITAL TERPILIH DI DAERAH MAKKAH, SAUDI ARABIA

ABSTRAK

Penggunaan agen antimikrobial yang berlebihan dan tidak sesuai serta kawalan jangkitan yang lemah menyebabkan masalah kerintangan, memanjangkan tempoh hospitalisasi, peningkatan kos perubatan, dan kematian. Program pengawasan antimikrobial (PPA) merupakan suatu usaha kolaboratif untuk mengoptimakan penggunaan agen antimikrobial dalam institusi penjagaan kesihatan melalui strategi meningkatkan kualiti berasaskan bukti. Justeru, matlamat penyelidikan ini adalah untuk menilai kesan pelaksanaan program pengawasan antimikrobial dalam penjagaan kritikal bagi mengoptimumkan penggunaan agen antimikrobial, menjimatkan kos dan meningkatkan hasil klinikal di hospital terpilih di Makkah, Arab Saudi. Kajian ini dijalankan dalam tiga fasa. Fasa pertama adalah pendekatan penerokaan untuk menentukan mikroorganisma morbiditi yang paling lazim dalam isolat darah bagi pesakit di wad umum dan unit penjagaan kritikal (ICU & CCU), serta corak kerintangan di kalangan komuniti yang diperoleh patogen yang diasingkan dari penduduk Makkah. Selain itu, fasa ini juga bertujuan untuk meneroka faktor-faktor risiko yang berkaitan untuk jangkitan nosokomial *Acinetobacter baumannii* (MDR-AB) yang tahan multi-ubat di hospital penjagaan tertiari, Makkah, Arab Saudi. Hasil kajian menunjukkan kejadian mikroorganisma Gram-negatif yang tinggi dalam CCU dan mikroorganisma Gram-positif dalam wad umum selama tempoh 12 tahun. Daripada 374 sampel isolat komuniti yang diperolehi, kerintangan tertinggi diperhatikan untuk amoxicillin / clavulanic acid. Dalam kajian kes kawalan yang dipadankan dengan hospital yang

dijalankan di hospital penjagaan tertiari, hasil regresi logistik pelbagai faktor risiko yang berkaitan dengan *Acinetobacter baumanni* (MDR-AB) tahan multi-ubat menunjukkan perkara berikut: pengimunotindasan (OR = 2.9; 95% CI 1.5-5.6; p = 0.002), hasil klinikal (OR = 0.4, 95% CI 0.3-0.9; p = 0.01), prosedur invasif (OR = 7.9; 95% CI 1.8-34.2; p = 0.002), kateter vena pusat (OR = 2.9, 95% CI 1.5-5.6; p = 0.000), dan tiub endotracheal (OR = 3.4; 95% CI 1.6-7.3; p = 0.001). Fasa kedua kajian mengukur tahap pelaksanaan dan keberkesanan program PPA di hospital-hospital di Makkah di peringkat farmasi dan di peringkat kebangsaan di kalangan pakar perubatan penjagaan kritikal KSA. Antara hospital yang mengambil bahagian, 19 (76 %), strategi yang paling lazim adalah, menghadkan formulari (90%) untuk agen antimikrobial spektrum luas dan penggunaan pesanan berhenti automatik (65%) untuk menghadkan terapi empirikal antimikrobial. Majoriti hospital tidak mempunyai garis panduan antimikrobial tempatan (90%) berdasarkan anti-biogram di seluruh hospital. Berdasarkan kaji selidik nasional di kalangan pengamal intensivis dewasa di ICU berasaskan universiti dan bukan universiti di Arab Saudi, dua puluh tiga (12%) unit rawatan intensif tidak mempunyai program Pengawasan Antimikrobial. Manakala, sebanyak 161 (88%) ICU mempunyai program Pengawasan Antimikrobial. Strategi pengawalan yang paling lazim digunakan adalah pemantauan pakar perubatan berjangkit bersama dengan pasukan ICU (59.3%), audit dan maklum balas oleh ahli farmasi klinikal (22.9%). Ketersediaan data kerintangan antimikrobial oleh ahli mikrobiologi klinikal kepada pakar perubatan dapat digunakan untuk membimbing terapi empirik bagi jangkitan di kalangan masyarakat. Berdasarkan hasil tinjauan kami, pengamal intensivis di Arab Saudi menyokong program pengawasan antimikrobial di ICU dan berpendapat bahawa PPA menyediakan perkhidmatan yang berguna kepada kedua-dua pihak pesakit dan doktor.Dalam fasa ketiga, strategi pengawasan

antimikrobial pelbagai disiplin dilaksanakan di penjagaan kritikal 20 katil di sebuah hospital terpilih di Makkah, Arab Saudi. Analisis siri masa pengubahsuaian kawalan digunakan untuk membandingkan hasil dalam tempoh 9 bulan sebelum dan selepas pelaksanaan PPA. Ubat-ubatan yang digunakan untuk profilaksis *Deep Vein Thrombosis* (contohnya perencat pam proton / penyekat reseptor H2) digunakan sebagai ubat pengesan bagi Kumpulan Kawalan. Purata penggunaan agen antimikrobial bulanan diukur sebagai *defined daily dose* (DDD) setiap 100 hari katil dikurangkan sebanyak 25% (742.86 vs. 555; $p<0.1$) berbanding dengan kumpulan kawalan (ubat pengesan) sebanyak 7% (35 vs. 38;$p<0.735$). Menariknya, terdapat kesan negatif ke atas kos dalam fasa pasca intervensi. Menariknya, penggunaan IV Ceftriaxone diukur sebagai *defined daily dose* (DDD) setiap 100 hari katil dikurangkan sebanyak 82% (94 vs 17; $p<0.008$), manakala penggunaan Vancomycin oral meningkat sebanyak 84% (27 vs. 172; $p< 0.0008$) di ICU. Kadar penerimaan doktor untuk majoriti cadangan PPA adalah signifikan. Cadangan utama untuk mengoptimalkan penggunaan antibiotik dalam penjagaan kesihatan adalah penglibatan pihak pentadbir tertinggi daripada pelbagai disiplin ke dalam jawatankuasa PPA, melaksanakan audit harian dan maklumbalas oleh ahli farmasi dan pakar perubatan klinikal dengan latihan penyakit berjangkit, aktiviti pendidikan berterusan mengenai penggunaan antimikrobial dan masalah kerintangan, melaksanakan penyelidikan, penggunaan garis panduan tempatan dalam mempreskripsikan antimikrobial berdasarkan kepada anti-biogram terkini dan sokongan daripada pasukan penjagaan intensif.

EVALUATION OF ANTIMICROBIAL STEWARDSHIP PROGRAMS IMPLEMENTATION AND OUTCOMES IN SELECTED HOSPITALS AT MAKKAH REGION, KINGDOM OF SAUDI ARABIA

ABSTRACT

Antimicrobial stewardship programs (ASPs) are collaborative efforts to optimize antimicrobial use in healthcare institutions through evidence-based quality improvement strategies. The aim of this research was to evaluate the impact of ASPs in a critical care setting for improving antimicrobial use, cost efficiency and clinical outcomes at selected hospitals in Makkah, Kingdom of Saudi Arabia (KSA). In phase one study, an exploratory survey approach was adopted to determine the presence of morbidity caused by organisms in both out and in-patients blood isolates at two Saudi hospitals. Besides that, resistance pattern among community acquired pathogens such as the Multi Drug Resistant *Acinetobacter Baumannii* (MDR-AB) was also documented. The findings from this phase suggested that there was high incidence of both gram positive and gram negative organisms in general wards over a 12 years period. In the same phase, results of multiple logistic regression of risk factors associated with Multidrug Resistant Acinetobacter baumanni (MDR-AB) were as follows: immunosuppression (OR = 2.9; 95% CI 1.5-5.6; p = 0.002), clinical outcome (OR = 0.4; 95% CI 0.3-0.9; p = 0.01), invasive procedure (OR = 7.9; 95% CI 1.8-34.2; p = 0.002), central venous catheter use (OR = 2.9; 95% CI 1.5-5.6; p = 0.000), and endotracheal tube use (OR = 3.4; 95% CI 1.6-7.3; p = 0.001). In the phase two study, a survey to explore current success and issues related to implementation of ASP programs in Makkah region hospitals at the pharmacy level (n = 23) and at the national level among critical care physician (n=382) were carried out. Among responding hospitals, respondents from 19 (76%) hospitals summarized ASP programs as following:

formulary restrictions (90%) for broad-spectrum antimicrobials and use of automatic stop orders (65%) to limit empirical therapy of antimicrobials. In national survey among practicing intensivists across Kingdom of Saudi Arabia (n= 382), the following output were obtained (Response rate: 39%; n= 149): 27 (18 %) of them mentioned that their intensive care units had no ASP implemented, while 122 (82 %) of them had reported that their ICUs had Antimicrobial Stewardship program in place. In phase 3, an evaluation of a multidisciplinary ASP implemented in a 20-bed critical care setting carried out. A controlled interrupted time series analysis was used to compare outcomes in the 9 months before and after ASP implementation. The findings found that the mean total monthly antimicrobial consumption measured as defined daily dose (DDD) per 100 bed days was reduced by 25 % (742.86 vs. 555; p = 0.1) compared to 7 % in the control group (tracer medications) (35 vs. 38; p = 0.735). Interestingly, there was a negative impact on cost in the post intervention phase. Interestingly, the use of IV Ceftriaxone measured as defined daily dose per100 bed days was decreased by 82 % (94 vs. 17; p = 0.008), whereas, oral Vancomycin use was increased by 84 % (27 vs. 172; p = 0.008) in the ICU. Overall, based on the present study findings, involvement of higher administration in multidisciplinary ASP committees, daily audit & feedback by clinical pharmacist and physicians with infectious diseases training, continuous educational activities about antimicrobial use and resistance, use of local antimicrobial prescribing guidelines based on up to date anti-biogram and support from intensive care team are key sets of recommendations that can be made to enhance quality use of antibiotics in Saudi healthcare institutions.

CHAPTER ONE: GENERAL INTRODUCTION

1.1 Background

Antimicrobial resistance (AMR) is a health risk worldwide and the main cause of health-related morbidity and mortality (J. E. McGowan, 2012). One reason is the development of MDR organisms (MDROs), which are associated with irrational and excessive antimicrobial prescribing behaviour (A. R. Marra et al., 2009). The incidence of MDROs is growing despite tight infection control strategies. Infections due to MDROs are associated with deterioration in clinical outcomes and increase the financial burden in healthcare settings. Cosgrove et al. found that cephalosporin-resistant *Enterobacter* infections enhanced mortality and the length of hospitalization and increased cost (Sara E Cosgrove, Kaye, Eliopoulous, & Carmeli, 2002). During hospitalization, up to 60% of all hospitalized patients in the United States received one dose of antibacterials during their stay. Up to 50% of such treatments are considered unnecessary or otherwise inappropriate, which may include the following (S. E. Cosgrove & Carmeli, 2003; Gerding, 2001; MacDougall & Polk, 2008; Vogtlander et al., 2004):

1. Treating non-bacterial infections
2. Treating colonization and contamination due to poor sampling technique
3. Recommending broad-spectrum antibiotics where narrow-spectrum drugs can be used effectively
4. Longer duration of therapy and
5. Lack of dose optimization, e.g., for vancomycin and aminoglycosides

Antimicrobial drug use is at least partially responsible for rising infections due to resistant organisms and has become a serious concern in the last decade (Sievert et al.,

2013). Additionally, resistance has emerged even to more potent organisms, e.g., Carbapenem-Resistant Enterobacteriaceae (CRE) and metallo-ß-lactamase-producing Enterobacteriaceae. These strains are responsible for 50% of the infectious disease-related mortality in the United States. In addition, these resistant strains carry genes that may transfer resistance to other antimicrobial agents (Ben-David et al., 2010).

The diminishing development of new antimicrobials and the emergence of resistance emphasizes that we must optimize the use of current antimicrobials via the implementation of surveillance programs, e.g., formulary restrictions and prospective auditing and feedback in healthcare institutions (Hersh et al., 2015; B. Spellberg et al., 2008). These approaches are supported by most of the official governing bodies in infectious diseases societies (B. Spellberg et al., 2011). Furthermore, in 2013, as per the Infectious Diseases Society of America (IDSA), to prolong antibiotic effectiveness, implementation of antimicrobial stewardship programs (ASPs) in healthcare institutions was one of the strategies to combat resistance (Bartlett, Gilbert, & Spellberg, 2013) and discourage the spread of resistant bugs in healthcare systems (Barlam et al., 2016; Dellit et al., 2007). Further, ASPs enhance the prescriber's adherence to treatment guidelines and result in appropriate antibiotics selection in clinical settings (Ansari et al., 2003; Bauer et al., 2010; Brink et al., 2016; R. Kaki et al., 2011).

Every institution uses a specific stewardship program with specific patient outcomes. The most common outcomes studied in various stewardship programs are a reduction in total antimicrobial use in an institution, decrease in inappropriate antimicrobial use, decrease in the infection-associated length of stay, decrease in infectious-related

mortality and decrease in overall AMR patterns in an institution (Jacobs, Kuper, Septimus, Arafat, & Garey, 2014; C. MacDougall & R. E. Polk, 2005)

Several surveys have been conducted globally and reported many types of antimicrobial stewardship strategies in health institutions. Howard et al., based on a globally administered survey, concluded that the majority (52%) of the institutions follow national prescribing guidelines and that most (58%) are implementing antimicrobial stewardship activities. Lack of personnel and information technology services were the major barriers in stewardship implementation (Howard et al., 2015).

1.2 Defining Antimicrobial Stewardship

Antimicrobial drugs are individual agents that do not directly affect patients while affecting the growth of microorganisms and thus curing infectious diseases caused by invading pathogens (C. Pulcini, 2014). Antimicrobial use is the key driver of AMR. Misuse of antibiotics, including unnecessary prescription and inappropriate use (inadequate dosing, incorrect pharmacokinetics and inappropriate duration according to patient characteristics) may lead to the development of AMR and is a major threat to public health. In 2003, Hecker et al. found that approximately 60% of the patients in the United States received at least one dose of antibiotics during hospitalization, and half of these instances were inappropriate (Hecker, Aron, Patel, Lehmann, & Donskey, 2003). Therefore, more prudent use of antimicrobial agents can slow or reverse the development of resistance (MacDougall & Polk, 2008). AMR is a considerable public health threat and is associated with a higher incidence of mortality and prolonged hospital stays. One of the reasons underlying this problem is the development of MDROs related to irrational and excessive prescriptions of antimicrobials (A. R. Marra et al., 2009).

This epidemic increase in antibiotic-resistant bacteria has led to the need to reduce excessive antibiotic use, especially during emergency department visits for community-acquired infections, e.g., acute respiratory infections, where a substantial number of antibiotics are prescribed for illnesses that do not require antibiotics clinically. Therefore, initial antimicrobial selection in acute care settings is of paramount importance in treatment success (Gonzales et al., 2001; S. Harbarth et al., 2003; M. Kollef, 2003; Kumar et al., 2006).

In recent years, there has been a rapid drop in antibiotic response against common infections. The diminishing investment in the development of new antimicrobials potentiates this concern and necessitates the adoption of strategies and programs in healthcare settings to optimize currently available antimicrobial use (Rice, 2008; Brad Spellberg, Powers, Brass, Miller, & Edwards, 2004). According to the Infectious Disease Society of America and the Society for Healthcare Epidemiology, the frequency of inappropriate antimicrobial use is a surrogate marker for the avoidable impact on AMR. Therefore, to promote the optimum use of antimicrobials and conserve their worth in healthcare settings, it is recommended by many regulatory agencies to develop a rational, systematic approach to the use of antimicrobial agents (Dodds Ashley, Kaye, DePestel, & Hermsen, 2014).

To achieve this goal and guide antimicrobial use through antimicrobial stewardship strategies, it is necessary to change the attitudes of prescribers (Friedman, 2013). The main paradigms of antimicrobial use include acute infections among outpatients and inpatients, chronic infections and veterinary medicine. Optimizing antimicrobial use in these disciplines requires knowledge of the outcomes associated with this misuse and

the effectiveness of strategies to overcome associated consequences (A. R. Marra et al., 2009).

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials (Fishman, 2012). ASPs are overarching programs of policies, management programs and control programs directed at improving antimicrobial use, resistance and clinical outcomes. Antimicrobial stewardship is a multidisciplinary approach involving multiple strategies to optimize antimicrobial use, e.g., dose optimization for antimicrobials based on drug pharmacokinetics/pharmacodynamics (PK/PD) programs, intravenous to oral switching of antimicrobials, de-escalation/streamlining of antimicrobials, and formulary restriction strategies (C. MacDougall & R. E. Polk, 2005; R. C. Owens, Jr., 2008). Therefore, establishing an ASP is of prime importance as it has great potential to promote judicious antimicrobial use in healthcare institutions.

1.3 Antimicrobial Stewardship Strategies

Every institution uses a specific stewardship program with specific patient outcomes. The most common outcomes studied in various stewardship programs are the reduction in total antimicrobial use in an institution, decrease in inappropriate antimicrobial use, decrease in infection-associated length of stay, decrease in infection-related mortality and decrease in the overall AMR pattern in an institution (Jacobs et al., 2014; Conan MacDougall & Ron E Polk, 2005; R. C. Owens, Jr., 2008).

Several surveys have been conducted globally and reported many types of antimicrobial stewardship strategies in health institutions. Howard et al., based on a global antimicrobial stewardship survey, concluded that national antimicrobial stewardship

standards were implemented in only 52% of the hospitals, while 58% were planning to implement antimicrobial stewardship activities in their institutions. Major barriers to ASP implementation were lack of personnel and lack of information technology. Antimicrobial restriction was the most implemented strategy among institutions with ASPs (Howard et al., 2015).

According to the IDSA, there are two core antimicrobial stewardship strategies: prospective audit with intervention, and feedback and formulary restrictions and preauthorization. Both strategies are proactive and are not mutually exclusive. Depending on the local practice patterns and resources, additional programs can be considered to gain maximum benefit from these strategies. Supplementary programs might include education, guidelines/clinical pathways, antimicrobial order forms, de-escalation of therapy, dose optimization, and IV to oral conversion (Barlam et al., 2016; Dellit et al., 2007).

The prospective audit is usually performed by an infectious diseases physician or clinical pharmacist and is an effective strategy to prevent excessive antimicrobial use. In some instances, such audits can be practised retrospectively to develop interventions based on findings in an institution. The main advantage of this strategy is to maintain prescriber autonomy and provide educational opportunities. One of the major drawbacks of this strategy is a reluctance of prescribers to change therapy if a patient is doing well on initial therapy, and the retrospective nature of the study permits inappropriate exposure. Furthermore, in some instances, it may be difficult to identify the decision-making team with this strategy (Dellit et al., 2007; Hermsen et al., 2014).

Formulary restriction and preauthorization are another highly recommended effective stewardship activity. The main objective of this strategy is to control the overuse of

broad-spectrum antimicrobials. Pre-authorization is required for most last-line antimicrobials to limit their misuse for severe infectious diseases. The most common disadvantage of this activity is the potential delay in therapy that may indirectly affect clinical outcomes. In addition, there is a limited role of infectious diseases physicians/clinical pharmacists in this strategy (Micek, Ward, Fraser, & Kollef, 2004).

In addition to the core strategies, there are additional recommendations that can support and facilitate the implementation of core strategies. National and international authorities recommend optimizing the knowledge of physicians through education about infectious diseases to promote prudent antimicrobial use (Barlam et al., 2016). Educational strategies can influence prescribing behaviour and promote the acceptance of antimicrobial stewardship in an institution. Most educational strategies often require a long time and consistency to achieve outcomes (Céline Pulcini & Gyssens, 2013). As per the WHO statement issued for the World Health Day 2011, educational strategies should target both patients and healthcare practitioners to prevent unnecessary antibiotic prescription (Leung, Weil, Raviglione, & Nakatani, 2011).

One type of evidence-based educational strategy is to create protocols to guide antimicrobial use for a given infection. This strategy can include the inclusion of locally developed guidelines based on specific patient populations and resistance patterns. The most important concern regarding pathways/guidelines is compliance, which in most cases is voluntary and depends on personal awareness. According to new international guidelines, there is a need for the on-going maintenance of pathways. The development of antimicrobial order forms can support guidelines and pathways for specific infectious diseases, e.g., pneumonia, sepsis, and surgical prophylaxis. Meyer et al. found that an implementation and enforcement of pneumonia treatment guidelines in

the ICU resulted in a 50% reduction in treatment duration and a 30% reduction in antibiotic consumption and costs. Connor et al. studied the consequences of a 72-hour automatic stop order and found it an effective strategy for antimicrobial stewardship (Connor et al., 2007).

Refailidis et al. provided an informative review of the optimal duration of therapy for acute respiratory infections based on a meta-analysis. He concluded that the duration of antimicrobial therapy could be shortened without compromising outcomes (Rafailidis, Pitsounis, & Falagas, 2009).

De-escalation, narrowing the spectrum of activity as appropriate based on culture/susceptibility results and clinical response, also supplements antimicrobial control. This activity may influence future prescribing patterns indirectly and can decrease inappropriate antimicrobial use while lessening the risk of adverse events. Physician resistance is a notable concern in this strategy, as prescribers may be reluctant to change therapy if the patient is doing well. In addition, there might be a chance of inappropriate narrowing of the spectrum based on the gram staining strategy (Drew et al., 2009; Eachempati, Hydo, Shou, & Barie, 2009; Rello et al., 2004). De-escalation also produces economic outcomes regarding cost minimization in antimicrobial therapy (Deresinski, 2007).

It is often a possibility that an antimicrobial is initiated appropriately and promptly but without pharmacokinetic and pharmacodynamic considerations. This may lead to the failure of therapy, as in many cases, there is a specific MIC (minimum inhibitory concentration) to eradicate the organism, minimize toxicity, and prevent resistance. Therefore, there must be a specific dose of antimicrobials based on pharmacokinetics parameters. This strategy will also impact future prescribing behaviour and thus limit

irrational antimicrobial use in acute care settings. In some instances, this strategy may enhance pharmacy and nursing time (DePestel et al., 2014; Lodise, Patel, Lomaestro, Rodvold, & Drusano, 2009).

1.4 Antimicrobial Stewardship in Critical Care Settings

Critical care facilities in healthcare institutions host most of the vulnerable patient population suffering from multiple disorders and having multiple catalysts to spread resistance, e.g., loss of physiological barriers and high antibiotic pressure. Furthermore, severe infections are most common in intensive care units and require careful management to improve patient outcomes. ASPs in critical care settings must ensure specific goals and strategies to promote rational antibiotic use promptly to treat life-threatening infections. An ICU ASP may exhibit some very ICU-specific goals and strategies (Brusselaers, Vogelaers, & Blot, 2011; Reham Kaki et al., 2011; Taggart, Leung, Muller, Matukas, & Daneman, 2015).

Antimicrobial stewardship implementation in intensive care units is quite challenging for the multidisciplinary team, e.g., I.D. physician, clinical pharmacist, and clinical microbiologists, as in critical care settings patient care involves a closed format where the intensivist takes responsibility for patient care and does not allow other professionals to intercede. Therefore, routine audit and feedback activity in clinical rounds is a suitable ASP activity in critical care settings. In addition, regular provision of AMR data and antibiotic use can develop a trust relationship in intensive care settings (M. H. Kollef & Micek, 2012; Kevin L Lawrence & Marin H Kollef, 2009; Taggart et al., 2015).

Timely recognition of infections is also a diagnostic challenge in critically ill patients, as signs and symptoms of inflammation might be conflated with infection signs and

mislead management. Clinical decision support and biomarkers triggering treatment algorithms are few advancements enabled by antimicrobial stewardship implementation in critical care settings. Clinical decision support to improve antimicrobial prescribing is evidenced by very limited studies. A landmark study by Evans et al., in Utah demonstrated the efficacy of CDSS in the ICU. The programs guide prescribing teams with antimicrobial selection and prompt feedback upon provision of patient's clinical data. Once the organisms is identified, recommendation for the correct choice of antimicrobial was provided by correlation with hospital based anti-biogram automatically. This program produced significant reduction in excessive drug dosages (87 vs. 405, $p<0.01$) and antibiotics susceptibility mismatches (12 vs 206, $P<0.01$). In addition, there was substantial reduction in the cost of antiinfective agents (adjusted mean, \$102 vs. \$427 and \$340, respectively; $P<0.001$), in total hospital costs (adjusted mean, \$26,315 vs. \$44,865 and \$35,283; $P<0.001$), and in the length of the hospital stay (adjusted mean, 10.0 vs. 16.7 and 12.9 days; $P<0.001$) (Evans et al., 1998). Further, viral infections are more common in critical care settings and need careful diagnosis to initiate antimicrobial therapy. The use of pro-calcitonin and C-reactive protein levels is another advancement in antimicrobial stewardship strategies to guide appropriate antibiotics therapy (Barlam et al., 2016; K. L. Lawrence & M. H. Kollef, 2009; Simon, Gauvin, Amre, Saint-Louis, & Lacroix, 2004; Singer et al., 2016).

In critical care settings, another challenge is the initiation of empirical antimicrobial therapy appropriately based on patient characteristics, site of infection, patient age, hepatic and renal function, previous antibiotics use and length of hospitalization. In addition, local colonization status with MDROs plays an important role in determining the initial antimicrobial therapy. Further, antimicrobial therapy in CCUs should be based on local anti-biogram-based treatment guidelines to prevent certain delays in

culture sensitivity results (Battleman, Callahan, & Thaler, 2002; Depuydt et al., 2006; Nseir et al., 2010).

As critically ill patients are haemodynamically unstable with variable organ functionality, the role of PK/PD is crucial in deciding patient-specific dosing. In PK/PD-optimized therapy, a stepwise approach is advised, e.g., selection of the PK/PD target for antibiotics and choosing pharmacokinetics-based loading and maintenance doses to sustain a steady-state plasma concentration of specific antibiotics. The PK/PD model is best applied to vancomycin and aminoglycoside antibiotics to achieve maximum therapeutic effects within a safe range (Roberts & Lipman, 2009; Tsai, Lipman, & Roberts, 2015).

Antimicrobial de-escalation is an approach to limit broad-spectrum antibiotics use and to target the causative pathogen. De-escalation is an important antimicrobial stewardship strategy in the ICU. However, de-escalation of current antimicrobial therapy is quite challenging in critical care settings, as intensivists are resistant to changing an effective broad-spectrum therapy. The sepsis campaign guidelines recommend initiating broad therapy within the first hour of the onset of sepsis and daily reassessment for potential de-escalation of therapy (Diane Ashiru-Oredope, Sharland, Charani, McNulty, & Cooke, 2012; Leone et al., 2014; Singer et al., 2016; Tabah et al., 2015). Therefore, de-escalation is a beneficial strategy in critical care settings to limit excessive broad-spectrum antimicrobial use.

The duration of antibiotics therapy in critical care settings is a striking ASP strategy if we want to reduce antimicrobial exposure in critically ill patients (Barrett, Edgeworth, & Wyncoll, 2015). It is also a challenging intervention in the ICU, as the patient may be improved from infection but not fully recovered from organ dysfunction. This phenomenon may mislead intensivists, and therapy might go beyond the required

duration. Therefore, implementation of biomarkers, e.g., serial pro-calcitonin and C-reactive protein measurement, can aid the ASP team to limit the length of antibiotic therapy. The cost-effectiveness of pro-calcitonin is still controversial, notwithstanding its effectives in limiting excessive antibiotic therapy. A multi-centre, prospective, parallel-group study conducted by Bouadama et al. concluded that "procalcitonin guided therapy in intensive care units may reduce antibiotics exposure and selective pressure without adverse outcomes" (Bouadma et al., 2010).

In conclusion, antimicrobial stewardship implementation in critical care settings involves special considerations regarding the patient population in such critical settings and requires an evidence-based approach to develop a trust relationship with intensivists. Therefore, for the successful implementation of an ASP, it is a prerequisite to assess current practice and antibiotics use and then define the importance of rational antibiotics use in critical settings. Consumption of restricted antibiotics such as carbapenems and glycopeptides, e.g., vancomycin, linezolid and colistin, measured as DDDs per 1000 patient days, will inform intensivists about ASP efforts and convince them of the value of ASP implementation.

1.5 Study Justification

Holy Makkah is of great importance in the Muslim world, and millions of pilgrims visit Makkah from various nations to perform Umrah and Hajj rituals. The majority of the pilgrims visit acute care settings and seek urgent care for acute infectious diseases, e.g., bronchitis, URTI, and community-acquired pneumonia (Z. A. Memish et al., 2014; S. Yezli, Shibl, Livermore, & Memish, 2012).

The most common causes of acute hospital admissions among Makkah residents, including pilgrims, are respiratory, cardiovascular, and gastrointestinal disorders. The highest incidence of admissions is related to respiratory disorders, including pneumonia

(39.4%) and the exacerbation of asthma and chronic obstructive pulmonary diseases COPD (14.4%). The most common comorbidities are hypertension, asthma, COPD, and diabetes mellitus (Al Shimemeri, 2012; Madani & Ghabrah, 2007).

The majority of antibiotics prescribed are for acute care, often as a treatment for respiratory tract infections, making them a major contributor to AMR. Resistance may result from the uncontrolled and indiscriminate use of antibiotics from this sector (Karabay et al., 2011).

To the best of our knowledge, there is limited literature describing the successful implementation and effectiveness of antimicrobial stewardship strategies in critical care settings in the KSA in general and in the Makkah region hospital settings dealing with Saudis and Hajj/Umrah pilgrim populations specifically. In addition, there are no data highlighting community-acquired AMR risk among Makkah residents. The general administration of pharmaceutical care in 2013 initiated the process of antimicrobial stewardship implementation at the Ministry of Health (MOH) hospitals primarily and later expanded it to all medical institutions. The administration has developed a five-year plan to implement stewardship in MOH hospitals. This program has completed the initial phases and is in the data-collection stage at selected hospitals, primarily in the central region in Riyadh and later to be completed in other regional hospitals (Alomi, 2017).

The whole scenario necessitates a detailed study of the prevalence of community-acquired organisms isolated from samples obtained from Makkah residents, including Hajj and Umrah pilgrims, suffering from community-acquired infections and their resistance pattern against commonly used antibiotics in order to develop an evidence-based ASP to treat common infections in critical care settings dealing with acute

admissions. The outcomes of the study will also be of pivotal importance to devise policies and strategies for antimicrobial stewardship implementation in other settings in the Makkah region.

1.6 Study Objectives

Phase 1: To determine the extent of antimicrobials reporting and community acquired resistance at selected hospitals in the Makkah region

i To assess the prevalence of bloodstream infection-causing pathogens and community acquired AMR for selected organisms at selected hospitals in Makkah, KSA.

ii To identify risk factors associated with MDR-AB nosocomial infections at a tertiary care hospital in Makkah, KSA.

Phase 2: To determine ASP success in hospitals in the KSA and their perceived level of success

i To identify ASPs in Makkah region hospitals and their perceived level of success.

ii To assess critical care physician knowledge, attitudes and perceptions of ASP implementation in critical care settings in the KSA.

Phase 3: Antimicrobial stewardship implementation in a critical care setting in a selected hospital in Makkah, Kingdom of Saudi Arabia

i To study the impact of ASP implementation on process, economical and clinical outcomes in a critical care setting by using a quasi-experimental study design in Makkah, KSA.

1.7 Thesis Overview

This thesis consists of nine chapters, covering an introduction, methods, results, and discussion. Chapter two, the literature review, starts with definitions of AMR mechanisms in bacteria and focuses on clinically prominent pathogens requiring attention at the global level. The chapter continues with an overview of antimicrobial stewardship core evidence-based strategies and their importance in clinical settings. Further discussion in this chapter proceeds with the role of the pharmacist in the efficient delivery of ASPs. The literature review finishes with a discussion of antimicrobial stewardship efforts at the global level and their relation to the current status of antimicrobial stewardship in the Middle East in general and in the KSA specifically. A detailed review of literature related to this study, looking at recent resistance threats and antimicrobial stewardship efforts in the KSA and elsewhere in the world, forms the bulk of this chapter.

Chapter 3 comprises a detailed discussion of the study methodology, and in particular, possible methodological approaches in each study phase to achieve study-specific objectives. Chapter three also highlights the study objectives according to the study phases. Chapters 4 and 5 are consolidated as phase 1 of the study to highlight antimicrobial use resistance patterns among isolated organisms from Makkah residents of multiple nationalities. Chapter four describes the findings related to commonly reported organisms in a tertiary care hospital and their prevalence in general wards and critical care areas and presents findings on the resistance patterns of community-acquired organisms isolated from Makkah residents attending two acute care settings for community-acquired infections. Chapter five presents findings from a matched case

control study addressing risk factors for MDR-AB-associated infections in the intensive care unit.

Chapters 6 and seven are consolidated in phase 2 of the study to highlight existing ASPs in the Makkah region and at the national level in critical care settings. Chapter six describes existing ASPs in the Makkah region and their level of success. Further, Chapter seven describes the knowledge, attitudes and perceptions of critical care physicians regarding ASP implementation in critical care settings at the national level. Findings from phase one and two form the basis for the implementation of ASPs in a critical care setting dealing with admissions from a pilgrim population in Makkah City.

Chapter 8 describes the intervention phase of the study. It describes the process of antimicrobial stewardship implementation in a critical care setting based on phase 1 and two findings. This chapter provides findings of the impact of implementation of ASP on process, clinical and economic outcomes. Lastly, Chapter nine draws the thesis to a conclusion with an overall summary, study limitations and a set of recommendations for further research.

CHAPTER TWO: LITERATURE REVIEW

2.1 Antimicrobial Resistance: A Global Healthcare Threat

2.1.1 Introduction

In recent years, there has been a rapid decline in the effectiveness of antibiotics in treating common infections, and with the influx of untreatable strains of CRE, we are almost at the brink of a post-antibiotic era. Below-optimum dosing of antibiotics facilitates the stepwise selection of resistance, and the spread is eased by inter-species gene transmission, poor hygiene and sanitation in communities and hospitals and increasing rates of global travel, trade, and disease transmission (Laxminarayan et al., 2013). Nosocomial infections have a significant role in the transmission of resistant organisms; however, community infections contribute equally, as nearly 80% of antibiotic prescribing is done at the community level. The majority of admitted patients continue to carry extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae over long periods (Arpin et al., 2003). The ESBLs are enzymes generated by gram-negative bacteria (GNBs) that arbitrate resistance to cephalosporins, penicillins, and monobactams. MDR ESBLs and carbapenem-resistant ESBL isolates pose substantial therapeutic challenges (Vaidya, 2011).

Mass gatherings such as the Hajj and Umrah may lead to serious health hazards from and among pilgrims via the transmission of diseases, especially infections that spread via contact, food or water contamination or respiratory droplets, an oral-faecal route or through vectors. Propagation of drug-resistant organisms during the Hajj is of the highest concern possible (Al-Tawfiq & Memish, 2015). During the Hajj, millions of pilgrims of multiple nationalities visit holy sites in Holy Makkah and Madinah. The

majority of the pilgrims are from Asian countries, e.g., India, Pakistan, and Bangladesh. Antibiotic resistance is a global issue but is quite prevalent in countries such as India, Pakistan, the KSA, Afghanistan, Bangladesh, and African countries (Atif H Asghar & Hani S Faidah, 2009; Idress, Mussarat, Badshah, Qamar, & Bokhari, 2010; Kader & Kumar, 2004; Oberoi, Singh, Sharma, & Aggarwal, 2013; Rath, Dubey, Sahu, Debata, & Padhy, 2014). There is a high risk of transfer of resistant organisms from pilgrims from such countries during travel. For instance, international transmission of New Delhi metallo-β-lactamase (NDM-1) has been confirmed in several countries (Nordmann, Poirel, Walsh, & Livermore, 2011), and ESBL bacteria transmission has been associated with international travel (van der Bij & Pitout, 2012). Therefore, it is imperative to highlight antibiotic use and resistance patterns among pilgrims to develop effective strategies to treat infectious diseases during the Hajj and Umrah season.

2.1.2 Mechanisms of Antimicrobial Resistance

Bacteria can develop resistance to antibiotics in several ways: intrinsic resistance to antibiotics or through spontaneous mutations in bacterial genes or the acquisition of new resistant genes. Intrinsic resistance is independent of antibiotic selective pressure and horizontal gene transfer. It may be associated with a lack of affinity of antibiotics for the bacterial site, the permeability of the drug into the bacterial cell or the presence of drug-destroying enzymes. In acquired resistance, previously sensitive bacteria develop resistance to antibiotics. This adaptation can be due to the mutation of a particular gene or transfer of a resistant gene via conjugation or transduction. Acquired resistance can be caused by the variable intracellular concentration of antibiotics due to low intake or increased efflux activity, genetic mutation of the bacterial chromosome and modification of the antibiotic by hydrolysis or modification of the binding site (A. H. Holmes et al., 2016; Principe et al., 2013).

In clinical practice, knowledge of the mechanism of resistance will ensure the optimal use of antibiotics and prevent the risk of acquired resistance. For example, polymyxin antibiotics are used as the last agent for many MDROs. GNBs, e.g., *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, acquire resistance against polymyxin antibiotics, whereas bacteria such as *Proteus* spp., *Serratia* spp., and *Burkholderia* spp. are naturally resistant to these drugs (Olaitan, Morand, & Rolain, 2014).

2.1.3 Antimicrobial Resistance among Gram-Positive and Gram-Negative Bacteria: Global Perspective

The declining usefulness of antibiotics in recent years and the introduction of CRE have nearly taken us to a post-antibiotic era (Jacob et al., 2013). In under-developed and developing countries, increased hospital stays and soaring rates of nosocomial infections are the major reasons for resistant strains and resistance. Moreover, mutations, irrational prescribing and suboptimum doses of antibiotics are contributing factors to resistance. Resistance is present on chromosomal and extra-chromosomal elements. The global spread of resistant clones, e.g., *Escherichia coli* ST131, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Klebsiella* ST258, are a few examples of this grave scenario (Laxminarayan et al., 2013).

The development of resistance in bacteria is evident from β-lactamases, with nearly 1000 types that incapacitate these β-lactam antibiotics (19). The spread of resistance genes such as Enterobacteriaceae generating ESBL, NDM-1, and *Klebsiella pneumoniae* carbapenemase (KPC) shows the ease of transmission of resistance. In this respect, healthcare facilities play a major role in the swift spread of resistant clones. Enterobacteriaceae resistance against carbapenem is rapidly increasing. Even in countries such as the USA, 4.6% of acute-care hospitals in 2012 reported at least one health-care linked infection from CRE (Jacob et al., 2013). This trend of booming

resistance is more prevalent in developing countries. For instance, the WHO-recommended ampicillin and gentamicin regimen for neonatal infections is encountering resistance, with 71% of *Klebsiella* spp. isolates and 50% of *E. coli* showing gentamicin resistance (Zaidi et al., 2005). ESBL production in *E. coli* has accelerated and is blunting second-line treatment with extended-spectrum cephalosporins. There are reports from Pakistan of pan-resistant CRE and *Acinetobacter* spp. (Perry et al., 2011; Saleem, Ahmed, Mir, Ali, & Zaidi, 2009). This resistance is also prevalent in Africa, with 50–60% of community-acquired gram-negative microbes such as *E. coli* linked with UTIs with resistance to amoxicillin, cefixime, and ciprofloxacin (Laxminarayan et al., 2013). Adding more problems to the situation are reports of NDM-1, first identified in 2011 in South Africa (Lowman et al., 2011).

Since 2000, there has been a global dissemination of ESBL-producing Enterobacteriaceae, largely through *E. coli* and *K. pneumoniae*. Typical ESBLs are plasmid-borne β lactamases conferring resistance to cephalosporins, penicillins, and monobactams. ESBL producers are inhibited by clavulanic acid in vitro. Enzymes triggering this phenotype are frequently of the CTX-M type, and *E. coli*-producing CTX-M are increasing in healthcare centres as well as at the community level globally. At present, more than one hundred types of CTX-M β-lactamases have been recognized that are grouped into five main categories on the basis of their amino acid sequences. The phenomenon of co-resistance to other antibiotics is another main issue related to these ESBL producers generating MDR strains. ESBL-producing *E. coli* are frequently resistant to trimethoprim–sulfamethoxazole, aminoglycosides and quinolones that have been reported from around the world. Mechanisms of resistance to quinolones in Enterobacteriaceae were considered to be only encoded on chromosomes, but the

appearance of the qnr (qnrA, B, C, D, S, and variants) gene family on plasmids and its global presence and reports in *E. coli* and *K. pneumoniae* are serious concerns. Plasmid-encoded qnr genes often co-exist with ESBL genes, and the horizontal transfer of plasmids harbouring these resistance genes concurrently may result in MDR strains (Balkhed et al., 2013).

The continuous spread of MDR pathogens globally is responsible for major clinical, humanistic and economic consequences. It is estimated that drug-resistant bacteria are responsible for one death every ten minutes in the United States and Europe because of the development of life-threatening infectious diseases (Harbarth et al., 2015). These pathogens are resistant strains of both gram-positive and gram-negative strains in addition to drug-resistant fungal organisms.

The most clinically important resistant gram-positive bacteria (GPBs) are MRSA and vancomycin-resistant enterococci. One of the reasons behind the spread of these pathogenic organisms is poor infection control measures at the hospital level (Organization, 2014). According to the European Centers for Disease Prevention and Control (CDC) AMR surveillance report in 2014, MRSA prevalence was decreasing in comparison to previous trends reported in 2012. A total of 6 out of 29 countries (Italy, Cyprus, Greece, Malta, Portugal, Romania) reported invasive MRSA isolates above 30%. In addition, vancomycin-resistant enterococci strains are reported more in Europe with strains of *Enterococcus faecium*. Ireland, Cyprus, Greece, and Romania particularly report rates of vancomycin-resistant *E. faecium* higher than 25% (De Kraker et al., 2013; Versporten et al., 2014).

Globally, the spread of MDR gram-positive organisms is limited due to various infection control measures and efficient interventions, e.g., hand hygiene campaigns

and reduced antibiotic selective pressure targeting gram-positive organisms (Eggimann & Pittet, 2001).

Resistance to gram-negative pathogens is surprisingly increasing worldwide, leading to outbreaks in a few countries, e.g., Greece, Italy, India, and others. Interestingly, resistance to carbapenems and colistin is the most challenging condition in healthcare (Ferri, Ranucci, Romagnoli, & Giaccone, 2017). In addition, GNBs have the ability to acquire genetic mutations via transformation from other resistant strains to develop high-risk clones and spread in various environments (Pitout, Nordmann, & Poirel, 2015).

The consensus of clinical microbiologists is that MDR GNBs pose an extreme danger to public health. The increased resistance of GNB is largely due to moveable genes carried by plasmids that may readily spread through bacterial populations. Furthermore, human air travel and movement permit the swift transport of bacterial plasmids and clones among regions and continents. Most of this distribution remains unnoticed, with resistant clones residing as part of normal human microbiota and detected only when they culminate in an endogenous infection (Kumarasamy et al., 2010).

Infections due to MDR gram-negative strains are associated with higher mortality rates (Vardakas, Rafailidis, Konstantelias, & Falagas, 2013) and fewer therapeutic choices. The last three options to treat MDR gram-negative infections are tigecycline, fosfomycin, and colistin. Despite the nephrotoxicity and neurotoxicity of colistin, it remains the drug of choice to treat fatal infections caused by MDROs, specifically in carbapenemase-endemic countries (Karageorgopoulos, Kelesidis, Kelesidis, & Falagas, 2008; Karaiskos & Giamarellou, 2014; Michalopoulos, Tsiodras, Rellos, Mentzelopoulos, & Falagas, 2005). Therefore, it is a serious option to limit multidrug resistance in gram-negative pathogens globally to optimize their therapeutic use in

treating life-threatening infections. Implementation of effective antimicrobial stewardship measures in community and healthcare settings can restrict the spread of MDR gram-negative pathogens worldwide. Timely delivery of antimicrobial diagnostic measures can play a synergistic role to achieve this goal (Roca et al., 2015).

2.1.4 Antimicrobial Resistance in the Kingdom of Saudi Arabia

As other continents, the KSA is at risk of AMR. Irrational antibiotics use and a large population of migrant workers specifically from the Indian subcontinent are the most prominent risk factors for the spread of MDR pathogens. In addition, antibiotic availability without prescription at the community pharmacy level positively contributes to inappropriate antibiotics use in the KSA (Emeka, Al-Omar, & Khan, 2014; Zowawi, 2016; Zowawi, Balkhy, Walsh, & Paterson, 2013). Zowawi et al. reported the high prevalence of ESBL- and carbapenemase-producing GNBs in Gulf Cooperation Council countries, including the KSA (Zowawi et al., 2013). A study from Jeddah reported a rate of 31% of ESBL-producing *E. coli* and *K. pneumonia* isolated from intensive care units (Rotimi, Al-Sweih, & Feteih, 1998). Yezli et al. reported conversion of carbapenems in Enterobacteriaceae in the KSA. In addition, resistance among *Pseudomonas aeruginosa* is increasing (Saber Yezli, Shibl, Livermore, & Memish, 2014). Furthermore, a study reported the finding of the mcr-1 gene in an *E. coli* strain from the KSA, Bahrain, and the United Arab Emirates (Sonnevend et al., 2016). Similarly, the KSA national surveillance of gram-positive cocci revealed that 32% of methicillin-resistant (MRSA) and 26% of *Streptococcus pneumonia* are resistant to erythromycin (Shibl et al., 2014).

A study conducted in a tertiary care hospital in Riyadh of ventilator-associated pneumonia patients determined the involvement of the most common pathogens and their resistance to commonly available agents. Interestingly, the authors found that

Acinetobacter baumannii was a highly resistant pathogen among isolates. *Pseudomonas aeruginosa* was the least-resistant pathogen except that it was completely resistant to ampicillin (Balkhy et al., 2014).

Mass congregations pose serious health hazards to attendees via the transmission of infectious diseases through contact, food or water contamination, respiratory droplets, and oral-faecal and vector-borne transmission. The potential for epidemics due to person-to-person contact and food- and water-borne disease eruptions may result in a rapid and broad geographic spread of diseases. Moreover, the introduction of non-endemic diseases is a feared event during such assemblies. Imported, exported and endemic are probable disease patterns during such gatherings. The Hajj is a unique mass congregation associated with substantial international travel. Millions of pilgrims around the world travel to perform Hajj and Umrah rituals in the holy cities Makkah and Madinah in the KSA. Each year, more than 5 million pilgrims from 184 countries around the world participate in the Hajj or Umrah, and during the Hajj, a huge number of pilgrims gather in close vicinity to perform mandatory rituals. While the Hajj is one of the most common repeated mass congregations, Umrah is a ritual performed by pilgrims throughout the year. The transmission of drug-resistant organisms during the Hajj is not well described. This obligation increases the risk of potentially dangerous transmissible diseases in this population. The stress on healthcare systems during these two holy rituals is enormous, and the difficulty in the communication of risk due to language and cultural barriers makes the scenario particularly challenging (Al-Tawfiq & Memish, 2015).

Recently, a systematic review conducted by Leangapichart et al. identified a high prevalence of third-generation cephalosporin-resistant bacteria among Makkah residents. In other studies, carbapenem-resistant bacteria were detected in *K.*